Rejections under 35 U.S.C. § 101

The Office is concerned that the pending claims lack utility. The Office asserts that "there is no objective evidence or any art of record to support the allegation that the claimed polypeptides would be therapeutic in the treatment of cancer or any other human disease (March 26, 2002, Office Action, Paragraph 3)." Applicants respectfully disagree. First, given that applicants claim nucleic acids encoding specific synMuv polypeptides having the ability to alter cell proliferation, the question is whether the nucleic acids have a credible utility, not the more specific question of whether they have utility for treating cancer or other human diseases. This being said, applicants direct the Office's attention to the M.P.E.P. (section 2107.02 III(A)) where it states.

> A. An Asserted Utility Creates a Presumption of Utility
>
> In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101...As the Court of Customs and Patent Appeals stated *In re* Langer:
>
> > As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Therefore, applicant is not required to provide evidence of utility, rather the Office must presume that applicant's disclosure of utility is sufficient, unless there is reason to question its veracity. Moreover, (M.P.E.P. 2107 II (D))

> Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless *countervailing evidence*

can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. (emphasis added)

The burden of proof, therefore, rests on the Office to provide objective evidence that the asserted utility of the instant invention lacks credibility. In fact, the Office has failed to provide such evidence, while applicants have provided strong and compelling evidence supporting the utility of the instant invention.

Declaration of Dr. H. Robert Horvitz

As additional evidence in support of the invention's utility, applicants provide the Declaration of Dr. H. Robert Horvitz. In his Declaration, Dr. Horvitz states that *lin-37* is useful as an agent for the modulation of proliferation. This is evidenced by the fact that that members of the *C. elegans* Class B synMuv gene pathway, to which *lin-37* belongs, function in a conserved tumor suppressor pathway and that *C. elegans* Class B synMuv genes function as negative regulators of the evolutionarily conserved Ras signal transduction pathway.

C. elegans Class B synMuv genes constitute a conserved tumor suppressor pathway. This is supported by the fact that many *C. elegans* synMuv genes have homology to mammalian genes known to be involved in cancer. For example, *lin-35*, a *C. elegans* class B synMuv gene, encodes a close homolog of mammalian tumor suppressor protein Rb. In humans, mutations in *lin-35* homolog, Rb, promote tumor formation, most commonly, retinoblastoma. The mammalian homolog of *lin-53*, another *C. elegans* class B synMuv gene, encodes Rb-binding protein, p48 (72% identity). In

addition, mammalian DP and E2F, homologs of *C. elegans* synMuv genes LIN-55 and E2F-1, function together to regulate the transcription of genes essential for cell cycle progression.

The *C. elegans* Class B synMuv genes, to which *lin-37* belongs, antagonize the Ras signal transduction pathway. The Ras pathway is conserved throughout evolution. In a variety of organisms, from *C. elegans* through humans, Ras regulates cell proliferation. For example, Ras activating mutations have been found in many human tumors. The importance of the Ras pathway in human oncogenesis is emphasized by the fact that Ras mutation frequency is among the highest of any gene associated with human cancer (Hunter et al., submitted with Reply to Office Action, mailed November 6, 2001).

In *C. elegans,* the Ras pathway is negatively regulated by the synMuv tumor suppressor pathway. Ras signalling controls vulval cell proliferation. Mutations in *C. elegans* synMuv genes result in a synthetic multivulva phenotype, characterized by excess vulval cell proliferation. Because the Ras pathway is highly conserved, insights gained into the regulation of *C. elegans* Ras will likely have important implications for the regulation of human Ras. It is likely that additional mammalian homologs of *C. elegans* synMuv genes will be identified, and that these genes will function in a mammalian tumor suppressor pathway that regulates Ras signalling.

C. elegans lin-37 is a Class B synMuv gene for which no mammalian homolog has yet been identified. In the nematode, *lin-37* antagonizes Ras signaling and functions in a tumor suppressor pathway to regulate vulval cell proliferation. Mammalian homologs of *lin-37* will likely antagonize Ras signaling and function in a mammalian tumor

suppressor pathway to regulate cellular proliferation. Thus *lin-37* and its mammalian homologs are likely to be useful in the treatment of a proliferative disorder (e.g., cancer).

Acceptance by Experts of the SynMuv Pathways Role in Cell Proliferation

As further evidence that synMuv genes (e.g., *lin-37*) are useful for the treatment of a proliferative disorder, such as cancer, and are so accepted by experts, applicants submit herewith the following references: Saito et al., "Malignant Worms: What Cancer Research Can Learn from *C. elegans,*" *Cancer Investigation*, 20:264-275, 2002 (Exhibit A); and Chang et al., "*C. elegans* Vulval Development as A Model System to Study the Cancer Biology of EGFR Signaling," *Cancer and Metastasis Reviews* 18:203-213, 1999 (Exhibit B); each of these references was written by a third party expert, and each accepts that mammalian homologs of *C. elegans* synMuv genes likely function in oncogenesis, and thus may be useful for the treatment of proliferative disorders, such as cancer.

Taking each in turn, Saito et al., provides a review of the usefulness of *C. elegans* in cancer research (page 264, first column third paragraph to second column).

> The purpose of this review is to explain the use of the model organism, *C. elegans*, and its relevance for cancer research. We discuss important contributions in three areas. First, homologs of human oncogenes and tumor suppressors have been found to act in genetic pathways that control well defined biological processes in *C. elegans*. Importantly, the gene networks elucidated in *C. elegans* appear widespread in the animal kindom and usually are similar to those used in humans. Thus, significant insights have been obtained into the function of human cancer genes by studying their counterparts in the nematode.

With respect to vulval cell fates, at page 270, first column, second and third paragraphs, and second column, first paragraph, Saito states:

> [T]he finding that the *C. elegans* Ras homolog functions in a growth-factor receptor signaling pathway that controls cell fate was an enormously important contribution to the studies of the *ras* oncogene.
>
> Many other genes have been found to regulate the *ras* signal-transduction pathway. Although their discussion goes beyond the scope [of] this review, it is important to mention that several of these genes are presently novel but will likely have mammalian counterparts. Thus, as soon as such mammalian genes are identified a candidate function is already available. Some of these genes may have roles in carcinogenesis. (Emphasis added.)

Clearly, Saito accepts that *C. elegans* genes that regulate Ras signal transduction, as *lin-37* does, are likely to play a role in mammalian cancer. Furthermore, with respect to applicants work on the synMuv genes (Lu et al., *Cell* 95:981-991, 1998), Saito states, at page 271, first column, line 6,

> [T]he *lin-35* class B product is similar to the retinoblastoma-susceptibility protein pRb. In addition, another class B gene, *lin-53*, encodes a protein similar to RbAp48 that interacts with pRb. It will be of great interest to determine whether homologs of the other synMuv genes act as tumor-suppressor genes in humans.

Clearly, Saito accepts that mammalian homologs of *C. elegans* synMuv genes are likely to function in mammalian cell proliferation.

Chang provides a review of the importance of *C. elegans* vulval development research in defining evolutionarily conserved signal transduction pathways for the study of oncogenesis. Chang states:

> Molecular genetic studies of *C. elegans* vulval development have helped to define an evolutionarily conserved signaling pathway from an EGF-like ligand through EGF receptor, Ras and MAP kinase to the nucleus. Further studies have identified novel positive regulators such as KSR-1 and SUR-8/SOC-2 and negative regulators such as cbl/SLI-1. The many negative regulatory proteins might serve to prevent inappropriate signaling, and thus are analogous to tumor suppressor genes. ...(Page 203, Abstract). (Emphasis added.)

And, at page 206, first column, third paragraph.

> Yet another set of apparently redundant negative regulators are known. Genetically, there are two classes of the so-called synthetic multivulva (synMuv) genes, class A and class B.

Chang therefore also accepts that mammalian homologs of *C. elegans* synMuv genes, which negatively regulate Ras signaling, are likely to act as mammalian tumor suppressor genes. Such genes would likely be useful for the treatment of a proliferative disorder, such as cancer.

As yet another line of evidence indicating that the synMuv genes (e.g., *lin-37*) would be considered by those of skill in the art to encode tumor suppressors useful in the treatment of a proliferative disorder, applicants further direct the Office's attention to the publication by Lu *et al.* (*Cell* 95:981-991, 1998) (Exhibit C). This publication by the inventors states, at page 987, second column, second paragraph, to page 988,

> *lin-35* encodes a protein related to Rb, and *lin-53* encodes a protein with striking similarity to an Rb-binding protein, p48 (72% identity). *lin-35*, *lin-53*, and a *C. elegans* histone deacetylase gene act in the same genetic pathway to antagonize a Ras signal transduction pathway in *C. elegans*. We propose that in mammals Rb, p48, and histone deacetylase genes act in a tumor suppressor pathway that involves mechanisms and molecules similar to those of the synMuv pathway in *C. elegans* and that may well antagonize a mammalian Ras pathway.

This work was peer-reviewed by top scientists and published in the prestigious journal *Cell*. The fact that researchers chosen to review articles for *Cell* were convinced that mammalian homologs of *C. elegans* synMuv genes encode proteins that likely function in a mammalian tumor suppressor pathway demonstrates that one skilled in the art believes that synMuv genes, such as *lin-37*, are useful in altering cell proliferation.

Summary

Applicants submit that *lin-37* functions in the *C. elegans* synMuv pathway, which is an evolutionarily conserved tumor suppressor pathway. In *C. elegans, lin-37* regulates the highly conserved Ras signal transduction pathway, and thus modulates vulval cell proliferation; mammalian homologs of *lin-37* will undoubtedly fulfill a similar regulatory function in mammalian cell proliferation. Moreover, the review articles submitted and the publication of the inventors work on synMuv genes in the prestigious journal *Cell* demonstrate that third-party experts agree that mammalian homologs of *C. elegans* synMuv genes are likely to be tumor suppressors.

Once more, applicants point out that no evidence has been made of record in this case that would cause one to doubt applicants' assertion that *lin-37* nucleic acids and polypeptides are useful for the modulation of cell proliferation. And, moreover, Applicants have provided compelling evidence from a number of sources supporting the utility of the instant invention. The utility rejection should be withdrawn.

Conclusion

If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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